Pharmacological Role of Dietary Polyphenols in Prostate Cancer Chemoprevention

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Abstract Prostate cancer (PCa) is the most common solid neoplasm and it is now recognized as one of the most important medical problems facing the male population. Due to its long latency and its identifiable pre-neoplastic lesions, prostate cancer is an ideal target tumor for chemoprevention. Different compounds of dietary origin are available on the market and certainly polyphenols such as epigallocatechin-3-gallate, curcumin, resveratrol, and the flavonoids quercetin and genistein represent those with supposed efficacy against PCa. As shown by many reports on PCa, the use of natural compounds could act against oxidative stress chronic inflammation. Basic research studies have revealed that polyphenols appear to act not only against oxidative stress but also impede pro-neoplastic cancer cell signaling. Although the current studies are limited, mechanisms of action of polyphenols have been confirmed, showing a promising future strategy in prostate cancer chemoprevention.

1 Epidemiology

Prostate cancer (PCa) is one of the most common cancers in men as reported by SEER statistics: in 2011 in the USA, there were more than 2.7 million people affected by prostate cancer with 233,000 new cases estimated during 2014 (Siegel et al. 2015). The trend in mortality for this cancer, due to amelioration of the diagnosis and treatment strategies, decreased during the last three decades and in 2014 it was about 5 % (Siegel et al. 2015).

PCa etiology has been not yet demonstrated, but several reports have linked chronic inflammation to its onset, and, in particular, the increase in oxidative stress could lead to higher expression of pro-inflammatory cytokines and growth factors. These mechanisms resulted in higher rates of cell division and therefore enhancing the possibility of incurring mutations (De Nunzio et al. 2011). Furthermore, the presence of proliferative inflammatory atrophy (PIA), precursor HGPIN, and prostate cancer may involve the presence of abnormal values of gene coding for

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Fig. 1 Polyphenolic phytochemicals in prevention of prostate cancer

glutathione *S*-transferase (GSTP1), gene coding for glutathione *S*-transferase A1 (GSTA1), and COX-2 (enzyme determining the conversion of arachidonic acid (AA) into the prostaglandin endoperoxide H2 precursors of PGD2, PGE2, PGF2α, PGI2, and thromboxane A2) (Cimino et al. 2014).

Based on these premises, polyphenols assume significance as constituents of chemopreventive fruits and vegetables worldwide for reducing the risk of cancer of various kinds including that of prostate (Fig. 1). Polyphenols occur naturally in different foods, and today there are more than 8000 divided into different subclasses of which the most represented are flavonoids, stilbenes, phenolic acids, and lignans (Ramos 2007). The importance of the polyphenols as anticancer substances shall be represented by the fact that they possess properties that act at different levels of molecular and cellular signaling.

2 Epigallocatechin-3-Gallate

Epigallocatechin-3-gallate (EGCG) represents the major polyphenol constituent present in green tea, the most popular beverage next to water. The tea plant (*Camellia sinensis*) has been cultivated in Asia for thousands of years and green tea has been used for centuries in China, Japan, and Thailand as a traditional medicine with a variety of applications (Abbas et al. 2013). Over the last two decades, many epidemiological studies have evaluated the chemopreventive properties of green tea, suggesting that increasing intake of green tea is correlated with significant decrease in the development of prostate cancer. The anticarcinogenic effects could be related to the inhibition of growth proliferation, induction of apoptosis, induction of phase II detoxifying enzymes, and reduction of oxidative damage to DNA as revealed by various in vitro and in vivo studies resulting in decreased risk and/or slower progression of prostate cancer with consumption of green tea (Khan et al. 2009). According to cell-culture studies, EGCG induced apoptosis and cell cycle arrest in many cancer cells without affecting normal cells. Particularly in PCa cells, EGCG activates growth arrest and apoptosis primarily via p53-dependent pathway that involves the function of both p21 and Bax such that

downregulation of either molecule confers a growth advantage to the cells. In androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells, EGCG inhibited COX-2 (inducible enzymatic isoform rapidly induced by growth factors, tumor promoters, oncogenes, and carcinogens) without affecting COX-1 expression at both the mRNA and protein levels (Khan et al. 2009). A study published in 2007 tested the effect of EGCG alone and in combination with specific COX-2 inhibitors on the growth and apoptosis induction of human prostate cancer cells both in vitro and in vivo. This study demonstrated a synergic action and an increased efficacy of selective COX-2 inhibitors in combination with polyphenols from green tea, inhibiting the growth of human prostate cancer cells. It was observed that this effect was mainly due to increased apoptosis from enhanced activation of caspase-6 and caspase-9 (Adhami et al. 2007). It has been shown that ester bond-containing green tea polyphenols, such as EGCG, potently and specifically inhibit the chymotrypsin-like activity of the proteasome in vitro and in vivo at the concentrations found in the serum on consumption of green tea, causing growth arrest in the G(1) phase of the cell cycle (Khan et al. 2009). In a study published in 2006, the combination treatment with EGCG, green tea extract, water extract of black tea, and theaflavins was shown to reduce gene expression and protein expression of androgen receptor in the athymic nude mice implanted with androgen-sensitive human CaP CWR22Rν1 cells that resulted in induction of apoptosis, decrease in the levels of VEGF protein, reduction in the level of serum PSA, and a reduced tumor volume (Khan et al. 2009; Siddiqui et al. 2006). Furthermore, this polyphenolic compound also seems to inhibit tumor expression of matrix metalloproteases (MMP-2 and MMP-9) and vascular endothelial growth factor (VEGF), which are overexpressed in angiogenesis and thereby prevent the invasion and the metastatic spread of cancer (Adhami et al. 2003). In a mouse model of orthotopic androgen-sensitive human PCa, the combination of soy phytochemical concentrate, black tea, and green tea significantly reduced tumor activity. This association synergistically inhibited tumor angiogenesis, final tumor weight, and metastasis and significantly reduced serum concentrations of both testosterone and dihydrotestosterone in vivo (Zhou et al. 2003). A prospective, double-blind, placebo-controlled study, using a defined product of green tea in capsule form in men with HGPIN, observed a 90 % reduction in developing PCa. This was the first study that has shown the effectiveness of green tea polyphenols for the treatment of premalignant lesions of prostate cancer (Bettuzzi et al. 2006). In the Japan Public Health Center-based prospective study, 49,950 men aged 40–69 completed a questionnaire on the basis of their green tea consumption habit. Consumption was associated with a dose-dependent decrease in the risk of advanced PCa. The multivariate relative risk was 0.52 for men drinking 5 or more cups/day compared with less than 1 cup/day (Kurahashi et al. 2008). However, further studies are needed so that the EGCG can be safely considered as potent chemopreventive agent for prostate cancer.

3 Curcumin

Curcumin (diferuloylmethane) is a major chemical component of turmeric (*Curcuma longa* Linn.) and it is used as a spice to give a specific flavor and yellow color to food in the Indian subcontinent (Khan et al. 2010). It has been used for centuries throughout Asia not only as a food additive but also as cosmetic and as a traditional herbal medicine to treat a variety of inflammatory conditions and chronic diseases. Over the past decades, several studies have substantiated the potential prophylactic or therapeutic value of curcumin and have unequivocally supported reports of its anticarcinogenic properties, such as its ability to influence a diverse range of molecular targets within cells. To date, no studies have reported any toxicity associated with the use of curcumin in either animals or humans (Goel and Aggarwal 2010). The chemopreventive properties of curcumin are attributed to its effect on several targets including transcription factors, growth regulators, adhesion molecules, apoptotic genes, angiogenesis regulators, and cellular signaling molecules. It has been shown that curcumin has the ability to induce apoptosis in both androgen-dependent and androgen-independent prostate cancer cells acting through the downregulating apoptosis suppressor proteins and other crucial proteins such as the androgen receptor. In PC-3 (hormone-independent line possessing dysfunctional androgen receptors) and LNCaP (hormone-sensitive cells), curcumin significantly altered microfilament organization and cell motility. In PC-3, human prostate cancer cell line, curcumin reduced MDM2 protein and mRNA and enhanced the expression of the tumor suppressor p21/WAF1, a gene that encodes a potent cyclin-dependent kinase inhibitor of cyclin–CDK2 and cyclin–CDK4 complexes, inducing apoptosis and inhibiting proliferation. Furthermore, curcumin inhibited androgen receptor-mediated induction of NKX3.1 expression and decreased the expression of androgen receptors and the binding activity to antioxidant response element directly (Khan et al. 2008). NKX3.1, a gene located nearly on 8p21.2, is involved in the initiation stage of prostatic tumorgenesis. There is considerable evidence that loss of NKX3.1 expression, along with PTEN heterozygosity, a gene that codes for a lipid phosphatase and functions as a negative regulator of phosphoinositol-3-kinase (PI3K) signaling, is found at high frequency in CaP (Syed et al. 2007). NKX3.1 gene encodes a homeobox-containing transcription factor that functions as a negative regulator of epithelial cell growth in prostate tissue. Thus, cellular NKX3.1 protein levels are critical for the maintenance of the prostate epithelial phenotype. Experiments conducted on LNCaP and PC-3 cells demonstrated that inflammation and in particular overproduction of TNF-α and IL-β lead to rapid ubiquitination and proteasomal degradation of NKX3.1 protein through phosphorylation of serine-196 (Markowski et al. 2008). In a study, it was found that treatment of prostate cancer cells with curcumin (1–100 μM) suppresses both constitutive (DU145) and inducible (LNCaP) NF-κB activation and potentiates TNF-induced apoptosis. Curcumin treatment (50–100 μM) induced apoptosis in both cell types, which correlated with the downregulation of the expression of Bcl-2 and Bcl-xL and the activation of

procaspase-3 and -8 (Mukhopadhyay et al. 2001). Moreover, a study previously showed that curcumin blocked the activation of L-mimosine or dimethyloxalylglycine treatment on PSA expression in human prostate carcinoma LNCaP cells (Chung et al. 2011).

In hormone refractory PCa, it was found that curcumin, in addition to conventional treatment, may decrease PCa aggressive proliferation and potentiate activity of taxane therapy increasing cytotoxicity and delaying prostate cancer cell resistance to these chemotherapeutic drugs (Cabrespine-Faugeras et al. 2010; Choi et al. 2008; Hour et al. 2002). In combination with radiation, curcumin (2–5 μM) showed significant enhancement of radiation-induced clonogenic inhibition and apoptosis in PC-3 cells and significant activation of cytochrome c and caspases-9 and -3. These mechanisms suggest that this natural compound acts by overcoming the effects of radiation-induced pro-survival gene expression in prostate cancer (Chendil et al. 2004). Others in vitro and in vivo studies have also demonstrated the inhibitory effects exerted by treatment with only curcumin against the growth and invasiveness of DU-145 prostate cancer cells. The inhibition of tumor cell invasion was due to reductions in MMP-2 and MMP-9. Curcumin was also shown to induce a marked reduction of tumor volume. This compound may therefore have a role as a chemopreventive agent and/or adjuvant therapy in the treatment of prostate cancer, probably as a nontoxic dietary supplement (Hong et al. 2006; Sharma et al. 2001). Until now, only few clinical data about curcumin have been obtained in humans, despite the large number of studies in in vitro and in animal models. In a pilot study of a standardized oral *Curcuma* extract, doses up to 180 mg of curcumin per day were administered to patients with advanced colorectal cancer for up to 4 months without overt toxicity (Sharma et al. 2001). A subsequent study has suggested that doses up to 8 g could be administered daily to patients with premalignant lesions for 3 months without overt toxicity (Chung et al. 2011). In a phase I clinical trial of oral curcumin, 15 patients with colorectal cancer refractory to standard chemotherapy consumed a capsule with a dose escalation between 0.4 g and 3.6 g daily for up to 4 months. A daily dose of 3.6 g curcumin was found to reduce 57–62 % of inducible PGE-2, suggesting a possible use of this compound for chemoprevention (Sharma et al. 2004).

4 Resveratrol

Resveratrol (*trans*-3,4,5-trihydroxystilbene, $C_{14}H_{12}O_3$) is a plant-derived polyphenolic phytoalexin produced by the enzyme stilbene synthase in response to infection by the pathogen *Botrytis cinerea* and to a variety of stress conditions, such as vicissitudes in climate, exposure to ozone, sunlight, and heavy metals. It exists in two isoforms: *trans*-resveratrol and *cis*-resveratrol where the trans isomer is the more stable form. Resveratrol is present in red grapes, peanuts, some common drinks, and dietary supplements. It has broad-spectrum beneficial health effects including anti-infective, antioxidant, and cardioprotective functions, but it has

gained considerable attention because of its potential cancer chemopreventive properties (Cimino et al. 2012). To this regard, resveratrol represents an ideal molecule, due to its relatively low toxicity and capacity to target multiple signaling molecules that collectively promote cancer cell survival and tumor growth. It was demonstrated that this natural compound can modulate many intracellular cancer targets, which affect cell growth, inflammation, apoptosis, angiogenesis, invasion, and metastasis. It is also able to potentiate the apoptotic effects of cytokines, such as TRAIL, chemotherapeutic agents, and gamma radiation (Cimino et al. 2012). Many in vitro studies have investigated the antiproliferative or proapoptotic effects of resveratrol in human prostate cancer cells, and its mechanism of action. Resveratrol was found to inhibit the growth of LNCaP cells (hormone sensitive cells), DU-145 (androgen-independent cells), and PC-3 (hormone-independent line possessing dysfunctional androgen receptors) in a concentration-dependent manner. It has also been shown to exert a strong inhibitory effect on the formation of free radicals in human macrophages, reducing oxidative stress within premalignant cells, and to reduce growth and spread of prostate cancer (Ratan et al. 2002). With regard to its proapoptotic effects, it has been shown to induce apoptosis in LNCaP and DU145 prostate cancer cell lines through different PKC-mediated and MAPK-dependent pathways (Shih et al. 2004). Furthermore, resveratrol-mediated apoptosis has been associated with p53 activation and also occurs via the death receptor Fas/CD95/APO-1 in various human cancer cells (Cimino et al. 2012). It is also possible that resveratrol exerts its chemopreventive action in part by modulating the expression or function of androgen receptor (Ratan et al. 2002). Another interesting chemopreventive mechanism related to this compound is represented by sensitization effect. Research from in vitro and in vivo studies indicates that resveratrol can overcome chemoresistance in tumor cells by modulating apoptotic pathways, downregulating drug transporters, modulating proteins involved in tumor cell proliferation, and inhibiting NF-κB and STAT-3 pathway (Cimino et al. 2012).

However, despite previous considerations, absorption of compounds should be evaluated before supposing a clinical effectiveness on human. In this context, Goldberg et. al. reported that after an oral dose of resveratrol (25 mg/70 kg), catechin (25 mg/70 kg), and quercetin (10 mg/70 kg) to healthy human subjects, these compounds appeared in serum and urine predominantly as glucuronide and sulfate conjugates and free polyphenols accounted for 1.7–1.9 % (resveratrol), 1.1–6.5 % (catechin), and 17.2–26.9 % (quercetin) of the peak serum concentrations and more than 80 % is absorbed. The absorption of transresveratrol was the most efficient as judged by peak serum concentration (16–17 % of dose consumed) (Goldberg et al. 2003; Vijayababu et al. 2006a).

These results support the hypothesis to use resveratrol as potentially chemopreventive drugs in prostate cancer patients, but clinical studies should be conducted to assess the real efficacy in humans.

5 Quercetin

Quercetin is the main representative of the flavonol class and antioxidant found in a variety of fruits and vegetables, highly concentrated in onions, broccoli, apples, grapes (red wine), and in soybeans (Vijayababu et al. 2006a). This flavonoid, besides having antioxidant and antiinflammatory activities, has been shown to possess potent antiproliferative effects against various malignant cells, although its molecular mechanism involved in chemoprevention of prostate cancer remains unclear in many respects (Vijayababu et al. 2006a). Quercetin treatment has been associated with selective antiproliferative effects and induction of cell death, predominantly through an apoptotic mechanism, in cancer cell lines. This compound seems to be able to induce apoptosis through multiple mechanisms: causing arrest in the G1 phase of the cell cycle or through interaction with cell cycle-regulated proteins, like cyclin D1 and CDK4; releasing cytochrome c and activating caspase-9 and caspase-3; through inhibition of PI3K, an enzyme involved in the pivotal cell survival pathway; and synergizing the effect of EGCG (Vijayababu et al. 2006a). Epidemiological studies and preliminary data have shown that quercetin inhibits the onset/growth of prostate cancer. It was noted that there is a 27 % risk reduction for prostate cancer for those who consume at least 24 μg of quercetin a day (Tang et al. 2010). In human prostate carcinoma LNCaP cells, quercetin inhibited the PI3K/Akt pathway, suppressed the phosphorylation of Bad, proapoptotic Bcl-2 family member, and subsequently altered the interaction between Bcl-xL and Bax, leading to cytochrome c release, activation of caspases, and consequently apoptotic death (Lee et al. 2008). It was also found that quercetin inhibits the proliferation of PC-3 cells causing a significant decrease in Cdc2/Cdk-1 and cyclin B1 protein expressions and increasing hypo-phosphorylated level of pRb and this may be attributed to decreased expression of growth responsive genes and subsequent growth inhibition of PC-3 cells (Vijayababu et al. 2005). Another important chemopreventive activity of quercetin might be to reduce the risk of prostate cancer metastasis. Tumor invasion and metastasis represent a multistep process that depends on the activity of many proteins. Proteolytic degradation of the extracellular matrix components is a central event of this process, primarily due to the action of matrix metalloproteinases. A study showed that this natural compound inhibits the expression of MMP-2 and -9 in prostate cancer cells (PC-3). As it has been detected that MMP-2 and -9 expressions were regulated by MAP kinase signaling pathways and quercetin is an inhibitor of several kinases including MAP kinases and tyrosine kinases, it is reasonable to speculate that quercetin might have downregulated the expression of MMP-2 and -9 through inhibition of protein kinases (Vijayababu et al. 2006b). In addition, quercetin appears to have the ability to suppress the function of androgen receptor, pivotal molecule in normal development of the prostate and in the development and progression of prostate cancer. Quercetin-mediated inhibition of the androgen receptor transcription activity in prostate cancer cells may be caused, at least in part, by the formation of a protein complex containing c-Jun, Sp1, and androgen receptor, but further

investigation will be necessary to examine whether other factors are also involved in this protein complex (Yuan et al. 2010).

6 Genistein

Genistein (4,5,7-trihydroxyisoflavone), the predominant isoflavone in human nutrition, is derived mainly from soybeans but also from other legumes, including peas, lentils, or beans (Perabo et al. 2008). Genistein has many important health benefits, such as lowering the incidence of cardiovascular diseases, prevention of osteoporosis, attenuation of postmenopausal problems, and reduction of body mass and fat tissue. It also has chemopreventive properties, and in particular genistein has been shown to inhibit growth of both androgen-dependent and -independent prostate cancer cells in vitro. Several mechanisms have been proposed for genistein-induced anticarcinogenic activity: inhibition of protein-tyrosine kinase, with the result of alleviating the growth of cancer cells by inhibiting PTK-mediated signaling mechanisms; inhibition of topoisomerases I and II and protein histidine kinase with antiproliferative or proapoptotic effects; antioxidant effects, through inhibition of the expression of stress response-related genes; inhibition of NF-κB and Akt signaling pathways, both of which are important for cell survival; the inhibition of angiogenesis; the downregulation of transforming growth factor-beta (TGF-β); and the inhibition of epidermal growth factor (EGF) (Zhao et al. 2009; Banerjee et al. 2008). In vitro studies have also demonstrated that this natural compound downregulates the androgen receptor of PCa cells via the estrogen receptor β, resulting in a modified response to hormonal stimuli, inhibits several steroid-metabolizing enzymes such as 5-α-reductase or aromatase creating a more favorable hormonal milieu and a protective effect against prostate cancer, blocks the cell cycle progression at G1, and inhibits PSA expression (Perabo et al. 2008). With regard to its modulation of antioxidant activity, a study examined the effect of genistein on human prostate cancer (LNCaP and PC-3) cells. The analysis of this study has shown that while the expression of many genes, including apoptosis inhibitor (survivin), DNA topoisomerase II, cell division cycle 6 (CDC6), and mitogen-activated protein kinase 6 (MAPK 6), was downregulated, the glutathione peroxidase (GPx)-1 gene expression level was upregulated with a subsequent increase of GPx enzyme activities (Suzuki et al. 2002). These results strengthen the hypothesis of a potential use of genistein in prostate cancer chemoprevention.

The tumor initiation and progression are often attributed to oxidative stress and the generations of ROS, which exceed cell ability to metabolize and detoxify them. In addition to causing genetic changes, ROS may lead to epigenetic alterations that affect the genome and play a key role in the development of human carcinogenesis (Campos et al. 2007). More specifically, ROS production is associated with alterations in DNA methylation patterns. Furthermore, ROS-induced oxidative stress can contribute to gene silencing by mechanisms that involve aberrant hypermethylation of tumor suppressor gene promoter regions and thus lead toward

progression to a malignant phenotype (Ziech et al. 2011). Oxygen radicals may cause damage to DNA and chromosomes, induce epigenetic alterations, interact with oncogenes or tumor suppressor genes, and impart changes in immunological mechanisms, like mutation of nuclear encoded genes, such as TP53, promotes carcinogenesis (Campos et al. 2007; Colotta et al. 2009). ROS are further determinant for the activation of inflammatory pathways that play a key role in cancer progression. Inflammation in cancer involves a close interplay between tumor-associated immune cells and the tumor cells themselves. Activation of NF-κB and AP-1 in immune cells, induced by ROS, determines production of inflammatory cytokines such as TNFα and IL-6 that have been demonstrated to be important in tumor progression (Wellen and Thompson 2010). Since ROS are considered key participants in the progression of cancer, the antioxidant effect of genistein might prevent tumor invasion or metastasis in prostate cancer cells by inhibiting production of matrix metalloproteinase, cell motility, and degradation of the basement membrane (Suzuki et al. 2002). The anti-metastatic potential of genistein was evaluated by a study through the development of an animal model, a murine model of human PCa metastasis. It has been demonstrated that genistein inhibits initial steps in the metastatic cascade, namely, cell detachment and cell invasion, and for the first time induces flattening of cell nuclei in vivo, a measure of increased cell attachment. Furthermore, genistein, through inhibition of phosphorylation, has been shown to inhibit activation of p38 MAPK and FAK (pro-motility proteins) in vivo, blocking cell motility. Genistein decreased metastases by 96 % and induced nuclear morphometric changes in PC3-M cells indicative of increased adhesion (i.e., decreased detachment) but did not alter tumor growth. This study showed for the first time that dietary concentrations of genistein can inhibit prostate cancer cell metastasis, but more specific analysis on the genistein effects upon human prostate cells is needed (Lakshman et al. 2008; Harper et al. 2009). Another interesting study has investigated the potential additive and synergistic effects of genistein and resveratrol for suppressing prostate cancer in the Simian Virus-40 Tantigen (SV-40 Tag)-targeted probasin promoter rat model, a transgenic model of spontaneously developing prostate cancer. It has been shown that high-dose genistein and resveratrol treatments, reducing cell proliferation and increasing apoptosis mainly through the modulation of sex steroid receptor and growth factor signaling, suppress the most severe grade of prostate cancer in these transgenic animals (Harper et al. 2009). In a randomized, placebo-controlled, double-blind phase II clinical trial, 54 study subjects were recruited and randomized to treatment with genistein 30 mg ($n = 23$) or placebo ($n = 24$) for 3–6 weeks prior to prostatectomy. It was shown that serum prostate-specific antigen (PSA) decreased by 7.8 % in the genistein arm and increased by 4.4 % in the placebo arm, without adverse events and with beneficial effect on blood cholesterol (Lazarevic et al. 2011).

7 Conclusion

In conclusion, the chemopreventive properties of dietary polyphenols are directed toward different molecular levels in prostate cancer. The primary action of these molecules may be reflected against oxidative stress. Furthermore, other evidences have confirmed that these compounds influence the growth of the prostate cancer by modulating cell survival signals and aiding in cell death pathways. Although a large number of studies have been conducted in vitro and in murine models, few clinical trials with well-defined concentrations of these compounds have been performed. Therefore, since the use of the polyphenols seems to have good perspectives, comprehensive randomized clinical trials are warranted in patients with prostate cancer to substantiate their benefits. However, regular consumption of diet rich in these polyphenols as reflected by the abovementioned studies presumably has the potential to lower the risk of prostate cancer.

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